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(54) Effervescent composition for oral rehydration.

(57) The invention relates to an effervescent product for the preparation of an oral rehydration solution for the treatment of diarrhoea. The product comprises oligosaccharides and/or disaccharides, and/or monosaccarides and/or amino acids as energy carriers, and (bi)carbonate and a bicarbonate precursor as alkalising substances.

The product has the form of a tablet or a powder.

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Effervescent composition for oral rehydration

The invention relates to an effervescent product for the preparation of an oral rehydration solution (OR-solution) for the treatment of diarrhoea.

Diarrhoea is not only a disease occurring frequently in man (for example children in developing countries), but diarrhoea also causes enormous economic losses in the (intensive) cattle breeding, notably in young calves and piglets. Diarrhoea also is a frequently occurring phenomenon in companion animals.

Diarrhoea is associated with loss of water (dehydration), loss of electrolytes (mainly Na^+, Cl^- and to a lesser extent K^+, HCO_3^-) and with a metabolic acidosis (acidification as a result of excessive lactic acid production).

The vast majority of the patients who do not survive the diarrhoea, die from dehydration, metabolic acidosis and/or disturbances of the electrolyte balance. Mortality can be prevented by treating these symptoms effectively. It has been found that the patient self often is able to eliminate the cause of the diarrhoea afterwards.

The cause of diarrhoea may be both infectious and non-infectious. Because the aetiology often is unknown and a causal treatment of the diarrhoea often is not possible a symptomatic treatment is indicated. Liquid therapy, preferably orally, is the first-choice therapy because it is effective both in bacterial, viral and non-infectious forms of diarrhoea. In this case it is not necessary to make the precise diagnosis.

The oral liquid therapy consists of the administration of an oral rehydration solution (OR-solution). This OR solution comprises water, electrolytes, absorption- promoting substances and alkalising substances, as a result of which dehydration, loss of electrolytes and acidosis are controlled effectively.

Because domestic animals suffering from diarrhoea very often are hypoglycaemic, the total energy content of the oral rehydration solution is of importance. The energy must preferable be present in the form of carbohydrates. The OR solution must be iso-osmotic; hypertonic solutions in fact cause an osmotic diarrhoea and delay the emptying of the stomach and hence the availability of the OR solution.

A citrate-containing effervescent tablet for the preparation of an oral rehydration solution for humane application is known from Scan.J.Infect.Dis. 18 (1986), pp. 65-70. The solution prepared by means of this effervescent tablet proved to be equally active for the treatment of diarrhoea in adults and children as the known bicarbonate-containing oral rehydration (OR) solution recommended by the World Health Organisation (WHO).

The above-mentioned effervescent tablet has the following compostion:

glucose (0 aq)	2182 mg
sodium chloride	421 mg
potassium chloride	180 mg
citric acid	691 mg
sodium bicarbonate	302 mg
saccharin sodium	50 mg

Dissolved in 120 ml of water the solution has the following composition:

Na^+	90 mmol/l
K^+	20 mmol/l
Cl^-	80 mmol/l
citrate (H_2 citrate$^-$)	30 mmol/l
glucose	100 mmol/l

This composition is substantially identical to the OR solution of the WHO, with the proviso that 30 mmol of citrate (H_2 citrate) have been used instead of bicarbonate.

The invention relates to an OR formulation which can be tabletted without any auxiliary substances (optionally lubricants may be added) by means of direct compression. The formed effervescent tablet dissolves completely without stirring in lukewarm water within a few minutes. Existing OR products are

commercially available in the form of powders packed in sachets, unsplit powders or unsplit liquid concentrates. The preparation of the OR-solution in this manner using these compositions is less simple than with the effervescent composition according to the invention.

In addition, the formed OR solution has been specifically prepared for use either in domestic animals or companion animals, this in contrast with most of the available OR products.

The resulting iso-osmotic OR solution comprises:

a. an electrolyte composition with which losses are compensated and with which a rapid rehydration is ensured.

b. lactose and/or maltodextrines as a result of which the required energy occupies a smaller ($\frac{1}{2}$ to 1/5) part of the osmotic space than when glucose alone is used.

c. a combination of directly and indirectly acting alkalising substances, as a result of which the metabolic acidosis is cured safely and effectively.

Usually the following auxiliary substances have to be used for the production of the effervescent tablets:

- bicarbonate (or carbonate salts)
- citric acid (or other solid organic acids, for example, gluconic acid, fumaric acid, maleic acid, tartaric acid, adipic acid).

Bicarbonate reacts with citric acid in the presence of water, citrate, H_2O and CO_2 being formed. As a result of the CO_2 development the effervescent effect occurs, as a result of which the tablet dissolves within a few minutes. With a strong effervescent effect a homogeneous solution is obtained without stirring.

Bicarbonate and citric acid are present in the oral rehydration effervescent tablet according to the invention not only as an "auxiliary substance", but also as a therapeutically active substance. As a matter of fact, the excess of bicarbonate and the formed citrate together form the mixture of directly and indirectly acting alkalising substances which are reponsible for the effective and safe neutralisation of the metabolic acidosis.

The OR solution which is obtained after dissolving the effervescent product has an ideal electrolyte composition, as a result of which the loss of electrolytes caused by the diarrhoea is fully compensated and the absorption of water from the intestine is optimally stimulated. Sodium ions play an important part in the absorption of water. By means of the absorption of sodium via active carriers an osmotic gradient is formed across the intestinal epithelium as a result of which water also diffuses passively. Therefore, the total quantity of sodium present in the OR product is of importance. The sodium concentration in the composition for the domestic animals is approximately 120 mmol/l, which is considerably higher than in the known OR products. Rehydration, therefore, will take place rapidly. Because a hypernatremia easily occurs in companion animals, the sodium concentration in this composition is 50-90 mmol/l.

During diarrhoea the potassium content in the plasma is increased. In fact, as a result of the metabolic acidosis an exchange of intracellular potassium and extracellular hydrogen ions occurs. In spite of this increased content of potassium in the plasma, OR solution must comprise potassium so as to replace for potassium lost via the faeces. Because during diarrhoea nett calcium is still absorbed and the body has the disposal of large reserve stocks, addition of calcium is not necessary. Magnesium may be added to OR solutions because small quantities of magnesium are lost.

The OR solution formed by means of the invention comprises a combination of so-called absorption-promoting substances. These are substances which promote the active absorption of sodium and hence also the absorption of water.

Glucose, but also galactose, promote the active sodium transport.

The up-take of sodium is also promoted by amino acids (L-configuration). There are probably several types of amino acid/sodium carriers in the intestine. In order to enable a maximum sodium up-take, the OR solution must comprise glycine or other amino acids. The sodium up-take in the intestine is also still promoted by, for example, bicarbonate, citrate and volatile fatty acids.

Absorption-promoting substances present in the solution prepared by means of the OR effervescent tablet are:

- glucose and galactose (splitting products of lactose) or glucose and glucose dimers (splitting products of maltodextrine)
- glycine.
- citrate and bicarbonate.

Because sodium and absorption promoting substances, for example, glucose, galactose and glycine, are preferably absorbed together by the active carrier systems in the intestinal epithelium, the molar ratio of substrate and sodium in the OR liquid has to be at least 1 : 1. Any excess of substrate will stimulate the absorption of endogenic sodium and water.

The total energy content of OR solutions is important because domestic animals suffering from

diarrhoea often are hypoglycaemic. The energy must be present substantially in the form of carbohydrates (for example, glucose). A 5% glucose solution which covers only a part of the energy need of the patient, however, is already iso-osmotic. Higher glucose concentrations give hypertonic solutions. Hypertonic solutions inhibit the stomach-emptying rate and hence the availability of the OR solution. Moreover they give rise to an osmotic diarrhoea. According to the invention this problem has been solved by replacing glucose by oligosaccharides and/or disaccharides. Oligosaccharides, for example, maltodextrines and disaccharides, for example, lactose, have a higher energy content (±5 to 2 times) than glucose, while the osmotic value per mol is equal. Maltodextrines are rapidly split in the intestines of monogastric animals to glucose and glucose dimers.

Young ruminants on the contrary are not capable of decomposing maltodextrines or other oligosaccharides because they do not dispose of the splitting enzymes α-amylase and maltase. Because (young) ruminants do have the disposal of the enzyme lactase, lactose has been chosen as the energy source in the composition for these animals. 1 Molecule of lactose is split by the enzyme lactase into 1 molecule of glucose and 1 molecule of galactose. By processing lactose and/or maltodextrines, more energy can be processed in an isotonic solution, so that a hypoglycaemia associated with diarrhoea can be controlled more effectively. Moreover, more "osmotic space" can be reserved in the OR solution for other components. For example, space has been reserved for extra glycine in the OR solution for companion animals. Recent (humane) research has demonstrated that glycine (110 mmol/l) not only promotes the absorption of sodium but also considerably reduces the duration of the diarrhoea.

Rehydration alone is not sufficiently capable of effectively correcting the metabolic acidosis as a result of which the patient is not or not sufficiently cured. It is therefore that the OR solution must comprise alkalising substances, for example, bicarbonate or "bicarbonate precursors". The direct alkalising activity of bicarbonate (and carbonate salts) is based on a neutralisation of hydrogen ions. The indirect alkalising activity of "bicarbonate precursors", for example, citrate, acetate and lactate, is based on the fact that the said substances are metabolised in the protonated form. As a result of the unique combination of direct (rapid) and indirect (slowacting) alkalising substances according to the invention, the metabolic acidosis associated with diarrhoea is effectively controlled without the risk of a hypokalemia (as a result of a too rapid exchange of intracellular H^+ ions against extracelular K^+ ions).

The commercially available OR products comprise either only bicarbonate (possibility of hypokalemia) or only "bicarbonate precursors" which have first to be metabolised before the acidosis can be controlled effectively (the activity often sets in only after a few hours). In addition, many commercially available ORS products comprise insufficient quantities of alkalising substances.

The oral effervescent tablet is particularly handy and simple to dose (1 tablet per litre for domestic animals and 1 tablet, for example, per 0.25 or 0.5 litre for companion animals).

The resulting iso-osmotic OR solution comprises:

a. an electrolyte composition with which losses are compensated and with which a rapid rehydration is ensured.

b. lactose and/or maltodextrines, as a result of which the required energy occupies a smaller ($\frac{1}{2}$ to 1/5) part of the osmotic space than with glucose alone.

c. a combination of directly and indirectly acting alkalising substances, as a result of which the metabolic acidosis is cured safely and effectively.

This combination of ideal electrolyte compositions, high energy-content and direct and indirect acting alkalising substances in an iso-osmotic OR-solution is unique.

The effervescent composition according to the invention has the following composition:

Component	Quantity (in mmol/unit of effervescent product necessary for the preparation of 1 litre of OR solution)
Sodium	50-150
Potassium	2-35
Magnesium	0-5
Calcium	0-5
Bicarbonate (or carbonate salts)	20-150
Citric acid (or other solid organic acid)	5-85
Maltodextrine (or another oligosaccharide)	0-100
Lactose (or other disaccharide)	0-200
Glucose (or other monosaccharide)	0-200
Glycine (or other amino acid or amino acid mixture)	0-120

The composition may be in the form of an effervescent powder or an effervescent tablet. A lubricant may be added for the manufacture of the effervescent tablet. An example of a composition of an effervescent tablet for veterinary application in (young) domestic animals is:

Component	Quantity (in g)
Sodium chloride	2.34
Potassium chloride	1.12
Sodium bicarbonate	6.72
Citric acid 0 aq	3.84
Glycine	2.25
Lactose	32.44

When this tablet is dissolved in one litre of water an OR solution is obtained of the following composition:

Component	Quantity (in mmol/l)
Na^+	120
K^+	15
Cl^-	55
Citrate $^{3-}$	20 [1)]
Bicarbonate $^-$	20
Glycine	30
Lactose	90 [2)]

1) equivalent with 20 x 3 - 60 mmol bicarbonate
2) equivalent with 90 mmol glucose + 90 mmol galactose

The pH of the resulting solution is weakly acid (approximately 6.4), which gives a good taste and shelf-life of the solution.

An example of a composition of an effervescent tablet for use in companion animals is:

Component	Quantity (in g)
Potassium chloride	0.56
Sodium bicarbonate	3.36
Citric acid 0 aq	1.92
Glycine	4.13
Maltodextrine	5.00
Glucose	5.28

When this tablet is dissolved in 0.5 litre of water an OR solution is obtained of the following composition:

Component	Quantity (in mmol/l)
Na^+	80
K^+	15
Cl^-	15
Citrate $^{3-}$	20 [1]
Bicarbonate $^-$	20
Glycine	110
Maltodextrine	10 [2]
Glucose	58.5

1) equivalent with 20 x 3 = 60 mmol bicarbonate
2) equivalent with 50-60 mmol glucose

Claims

1. An effervescent product for the preparation of an oral rehydration solution, characterised in that it comprises oligosaccharides and/or disaccharides, and/or monosaccharides and amino acids as energy carriers, and (bi)carbonate and a bicarbonate precursor as alkalising substances.

2. A product as claimed in Claim 1, characterised in that it comprises maltodextrine and/or lactose or sucrose and/or glucose or galactose as (an) energy carrier(s).

3. A product as claimed in Claim 1, characterised in that it comprises bicarbonate or carbonate and citric acid or other solid organic acids as alkalising substances.

4. A product as claimed in Claims 1-3, characterised in that it is in the form of an effervescent tablet.

5. A product as claimed in Claims 1-3, characterised in that it is in the form of an effervescent powder.

6. A product as claimed in Claims 1-3, characterised in that it has the following composition per unit of effervescent product necessary for the preparation of 1 litre of OR solution:

Component	Quantity (in mmol/unit of effervescent product necessary for the preparation of 1 litre of OR solution)
Sodium	50-150
Potassium	2-35
Magnesium	0-5
Calcium	0-5
Bicarbonate (or carbonate salts)	20-150
Citric acid (or other solid organic acid)	5-85
Maltodextrine (or other oligosaccharide)	0-100
Lactose (or other disaccharide)	0-200
Glucose (or other monosaccharide)	0-200
Glycine (or other amino acid or amino acid mixture)	0-120

7. A product as claimed in Claim 4 for (young) domestic animals, characterised in that it has the following composition:

Component	Quantity (in g) (for 1 litre of H_2O)
Sodium chloride	2.34
Potassium chloride	1.12
Sodium bicarbonate	6.72
Citric acid 0 aq	3.84
Glycine	2.25
Lactose	32.44

8. A product as claimed in Claim 4 for companion animals, characterised in that it has the following composition:

Component	Quantity (in g) (for 0.5 litre of H_2O)
Potassium chloride	0.56
Sodium bicarbonate	3.36
Citric acid 0 aq	1.92
Glycine	4.13
Maltodextrine	5.00
Glucose	5.28

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EUROPEAN SEARCH REPORT

Application Number

EP 90 20 0257

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	WO-A-8[illegible]501 441 (GJERLOV) * Page 1, lines 1-9; page 12, example 2; claims 11,12 *	1-6	A 61 K 9/46 A 61 K 33/14
A	"Dictionnaire Vidal", 64th edition, - 1988, pages 69,70,86,88,89, OVP, Paris, FR * Pages 88,89 "milupa EES 45"; page 86, "Lytren"; pages 69-70 "Gallialite" *	1-8	
A	FR-A-2 467 599 (INRA) * Page 7, example 1; page 9 *	7,8	
A	EP-A-0 219 337 (NICHOLAS KIWI (PACIFIC)) * Page 11, example 5 *	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K
A 23 L

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	10-05-1990	BENZ K.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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